REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Applicants and its undersigned representative wish to express their appreciation to the Examiner for his courtesy and consideration provided to the Applicants during the telephonic interview held on January 13, 2004.

Claims 18, 26-29, 31-35, 37-58, 60-69 and 71-75 are pending after the foregoing amendments. Claims 18, 71 and 72 are withdrawn. The remainder of the claims are rejected.

The subject matter of claim 36 is incorporated into claim 26. Claim 36 is accordingly cancelled. Entry of this amendment is considered appropriate, even though the action is final, since the subject matter of the amendment has been previously considered by the Examiner.

There are two grounds of rejection.

Claim 59 is cancelled without prejudice to expedite allowance, in view of the fact that the remainder of the claims generically cover the Campath-1 antibody.

The rejection of claim 59 under 35 USC 112, first paragraph, is thus deemed to be overcome.

Lastly, the rejection of claims 26-29, 31-69 and 73-75 under 35 USC 103 as unpatentable over Isaacs et al. in view of Carter et al. and Riechmann et al. is respectfully traversed as applied to the claims as amended.

Isaacs et al. teach that tolerance induction equivalent to that induced by an isotype matched irrelevant antibody can only be achieved by administrating a combination of two non-

cell binding mixed molecule antibodies.

Carter et al. teaches that replacing entire CDR regions of an antibody can be used to establish which CDR(s) is/are binding to antigen. This is achieved by replacing each CDR from the antigen-binding antibody with a neutral (human) CDR. This is enabling for facilitating or improving the humanization process.

It is important to note that Carter et al. was concerned with the (then and now) established objective of creating an antibody that is accepted by the host, via humanization. That is, creating an antibody that is almost entirely, or predominantly, human and, consequently, the human host being naturally tolerant of human immunoglobulin frameworks, is unable to respond against it. This is fundamentally different from the object of our application, which is concerned with reprogramming the human host not to respond to an antibody. Essentially, akin to a "negative vaccine" whereby the antibody is being used to actively make the host tolerant. Thus, we are removing cell-binding (function) but retaining immunogenic residues/regions intact (to facilitate tolerogenicity). Indeed, the technology described in our application may be applied to any protein, whereas Carter et al. can only be applied to antibodies. Thus, Carter et al. actually teaches one skilled in the art away from using the negative vaccine approach of our invention.

Issacs et al. use a mixed molecule, whereby replacing either the entire heavy chain or the entire light chain with irrelevant H & L chains created the two different non-cell binding antibodies (YTS169.4GL & YTS169.4HK respectively). The strategy of employing one of these non-cell binding antibodies as a tolerogen was insufficient; both non-cell binding mixed molecule antibodies were necessary for tolerogenicity. Furthermore, Isaacs et al. did not teach

how much modification of the therapeutic antibody would be necessary to achieve both non-cell binding and tolerance induction properties in a single tolerogenic antibody. Indeed, Isaacs et al. infers that substantial modifications would be necessary – as noted by the requirement that both non-cell binding antibodies were necessary for induction of tolerogenicity.

Although one skilled in the art might have combined Isaacs and Carter, since each one directs away from our present invention it is unlikely that one skilled in the art would be sufficiently motivated to try and modify a therapeutic antibody to achieve non-cell binding and tolerance induction properties. Indeed, even if one skilled in the art at that time had pursued this approach it would have been with the understanding that an unknown but significant modification of the native therapeutic antibody would be necessary to achieve both non-cell binding and tolerance induction.

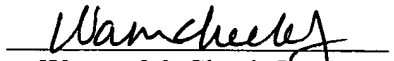
As explained by Professor Waldmann during the telephonic interview, the present inventors surprisingly discovered that a very limited number of mutations to the variable domains of a therapeutic antibody can achieve excellent non-cell binding as well as tolerance induction properties. This discovery was totally unexpected at the time of the invention. One skilled in the art could not have had any reasonable expectation that the claimed antibody, having variable domains with greater than 90% sequence identity with the variable domains of the therapeutic antibody, would have both excellent non-cell binding and tolerance induction properties. It could not have been predicted from the cited references that modification of less than 10% of the amino acids of the variable domains of a therapeutic antibody would create an antibody which has affinity for antigen binding reduced to 50% or less as compared to the therapeutic antibody due

to the modification, and yet also still induce excellent immunological tolerance to the therapeutic antibody.

Accordingly, it is respectfully submitted that the claims as amended are patentable over the cited references, thus reconsideration and allowance is respectfully solicited.

Respectfully submitted,

Herman WALDMANN et al.



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